REMARKS

Upon entry of the foregoing amendment, claims 2-12, 16-22, 25, 26 and 28-38, 42, 43, and 45-52 are pending in the application, with claims 1, 13-15, 23-24, 27, 39-41 and 44 canceled without disclaimer of, or prejudice to, the matter as originally claimed. Although claims 1-27 have been withdrawn by the Examiner under 35 U.S.C. § 121, Applicant had previously amended method claims 2-12, 16-22, 25 and 26 to include the limitations of the product claims such that upon allowance of the product claims, the method claims may be rejoined. Currently, claims 28-38, 42-43, and 45-52 stand rejected under as allegedly being obvious under 35 U.S.C. § 103 (a).

Independent claims 30 and 42 are amended to improve the syntax of the claims to further clarify that the compositions of the present invention are able to induce apoptosis in both androgen responsive and androgen independent prostate cancer cells and that treatment of prostate cancer cells with the compositions of the present invention is more effective than the additive effect of treatment of prostate cancer cells separately with TRAIL and an antiprogestin. Other amendments (e.g., claims 45, 47, 49-51) are made to remove terms for which there is no longer antecedent basis as a result of previously entered amendments. Support for the amendment of the claims is found ii the specification at page 18, lines 18-27, and Figure 1, describing the synergistic effects of using TRAIL and an antiprogestin. Accordingly, no new matter is added by the amendments to the claims.

Interview Summary

A telephone interview regarding outstanding issues in the case was conducted on June 18, 2006. Present at the interview were the Examiners, Mr. Jeffrey Siew, and Ms. Minh-Tam Davis, the inventor, Dr. Vijay Kumar, and the Applicant's representatives, Ms. Cynthia B. Rothschild and Mr. Benjamin Schroeder. Issues discussed were the standing rejection of the claims under 35 U.S.C. § 103(a). Applicant's representatives presented arguments that the cited references did not provide a motivation or suggestion to combine the references as is required to find *prima facie* obviousness. Thus, arguments were presented that there was no suggestion in the cited references that Mifepristone, as compared to the many other chemotherapeutic agents known in the art,

would be expected to act with TRAIL in a manner to increase cell death in both androgen-sensitive and androgen-insensitive prostate cancer cells. Additionally, arguments were presented that the secondary consideration of the unexpected synergism between TRAIL and Mifepristone provided additional evidence that Applicant's invention is not obvious under 35 U.S.C. § 103(a). The Examiners indicated that Applicant's arguments presented valid considerations. It was suggested that Applicant's arguments should be presented as a written response and would be given careful consideration.

The Applicant and Applicant's representatives thank the Examiners for conducting the interview and helping to resolve the outstanding issues in the case.

The Rejection of the Claims Under 35 U.S.C. 103 is Traversed or Rendered Moot

A. Prima Facie Obviousness

The Examiner rejected claims 28-38, 42-43, and 45-52 under 35 U.S.C. 103(a) as being allegedly unpatentable over Bonavida, B. et al., 1999, Oncology 15(4):793-802 (hereinafter "Bonavida"), Yu et al, 2000, Cancer Res., 60:2384-2389 (hereinafter "Yu"), or Gliniak, B., et al., 1999, Cancer Res., 59:6153-6158, (hereinafter "Gliniak"), in view of Fathy El Etreby et al., 2000, The Prostate 42: 99-106 (hereinafter "El Etreby"), or Kiode, S.S., et al., J. Reproductive Medicine, 1998, 43:551-560 (hereinafter "Kiode").

Applicant has previously amended the claims to describe that the compositions of the present invention are able to treat prostate cancer that includes both androgen responsive and androgen independent prostate cancer cells, and that treatment of prostate cancer cells with the compositions of the present invention is more effective than the additive effect of treatment of prostate cancer cells separately with TRAIL and an antiprogestin. Applicant respectfully asserts that there is no suggestion by the references, either alone or in combination, that combining TRAIL with an antiprogestin would be effective in prostate cancer cells, such as LNCaP cells, that are refractory to treatment by either TRAIL or an antiprogestin, or that the combination of TRAIL and Mifepristone would be more effective than the additive effect of the TRAIL and the antiprogestin separately applied to the cancer cells.

Applicant again respectfully asserts that the Examiner has not established a *prima facie* case of obviousness. The Federal Circuit has stated that "[i]n order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method." *Motorola, Inc. v. Interdigital Technology Corp.*, 43 U.S.P.Q. 2d 1481, 1489 (Fed. Cir. 1997) (quoting *Beckman Instruments, Inc. v. LKB Produkter AB*, 13 U.S.P.Q. 2d 1301, 1304 (Fed. Cir. 1989)). Also, subsection 706.02(j) of the MPEP states that to establish a prima facie case of obviousness three criteria must be met:

(i) a suggestion or motivation to modify or combine references;

(ii) a reasonable expectation of success; and

(iii) all the limitations in the claim(s) must be taught or suggested by the reference, or combination of references.

The Applicant respectfully asserts that the cited references do not provide a motivation or suggestion to combine the references.

Bonavida

The Examiner cites Bonavida as teaching two strategies that can be used to sensitize resistant cancer cells to TRAIL-mediated apoptosis: (1) the suppression of an anti-apoptotic molecule; or (2) the up-regulation of a pro-apoptotic molecule. Bonavida describes TRAIL in combination with cyclohexamide (an inhibitor of protein translation) in melanoma, adriamycin (an antibiotic) in multiple myeloma, or actinomycin D (a terminator of transcription) in certain prostate cancer cell lines. It is not suggested by Bonavida that a compound that has a hormone receptor-mediated function, such as an antiprogestin, would be expected to target apoptotic machinery so as to overcome a cell's resistance to TRAIL. Also, with respect to prostate cancer, Bonavida shows, in contrast to Applicant's invention, that there is no correlation between expression of TRAIL death receptors (DR4, DR5, DcR1 and DcR2) in the cancer cells and the sensitivity of the cells to killing by TRAIL. Bonavida at Table IV, page 799. In contrast, Applicant shows that the effects of TRAIL and Mifepristone in prostate cancer cells are mediated by death receptors. See the Specification at Figure 2 and related text at pages 19-20.

Thus, Applicant respectfully asserts that Bonavida suggests only that certain relatively nonspecific agents may be combined with TRAIL to increase cell killing, as

Bonavida describes using TRAIL with chemotherapeutics that work by different (and more generalized) biochemical pathways (e.g., actinomycin D, adriamycin, and cyclohexamide) than antiprogestins. Bonavida does not, however, suggest that these general chemotherapeutic agents would act in a manner similar to an antiprogestin to induce cell death in prostate cancer.

Gliniak

Gliniak describes the use of TRAIL in combination with a topoisomerase inhibitor, camptothecin or CPT-11 (a water soluble analogue of camptothecin), to treat colon cancer. However, Applicants specifically note that Gliniak also teaches that many other chemotherapeutic agents, including cisplatin, 5-fluorouracil, mitomycin, etoposide, or Adriamycin (in contrast to Bonavida above), all of which would be expected to have the ability to reduce apoptosis by inhibiting synthesis of apoptotic cellular machinery (e.g., enzymes, receptors, and the like), did not result in an enhancement of cytotoxic activity by TRAIL. Gliniak at page 6154, column 2. Further, although Gliniak postulates that the tested topoisomerase inhibitors act to inhibit the synthesis of an apoptotic protein, Applicant notes that there is no measurement of apoptosis in any of the studies presented by Gliniak. A careful reading of Gliniak does not provide any suggestion for the combination of TRAIL with other chemotherapeutic agents other than topoisomerase inhibitors, since all of the other chemotherapeutic agents that were tested did not work. Thus, Applicant respectfully maintains that Gliniak, in providing evidence that topoisormerases, but not other chemotherapeutic agents, can be used to enhance TRAIL, teaches away from Applicant's invention. Additionally, Applicant maintains that studies in colon cancer (or other types of cancer) provide little basis for treatment of prostate cancer, due to the very different nature of cancer biology in different cell types.

Yu

Yu describes that TRAIL can induce apoptosis in certain androgen-insensitive prostate cancer cells that are known to be sensitive to TRAIL, and explores cellular mechanisms by which TRAIL may inhibit apoptosis. Yu, in contrast to Bonavida, indicates that sensitivity to TRAIL-mediated apoptosis is mediated by death receptors. Yu at pages 2386-87, Figure 3. Thus, Yu teaches away from Bonavida and one would not be motivated to combine the teachings of the two references to develop a

chemotherapeutic compound. Yu is completely silent about the ability of other agents to increase TRAIL-mediated apoptosis. Applicant maintains that Yu, like Bonavida and Gliniak, does not describe, teach or suggest a mechanism by which antiprogestins would be able to increase the effectiveness of TRAIL so as to provide greater than additive effects for the induction of cell death. Nor does Yu provide a basis for suggesting how TRAIL may be used to induce cell death in prostate cells that are insensitive to TRAIL.

Koide

Applicants respectfully maintain that Koide does not add to the deficiencies of the TRAIL references (i.e., Bonavida, Gliniak, and Yu). Koide provides no basis for inferring that Mifepristone could act in combination with TRAIL to influence the level of apoptosis in prostate cancer cells even when read in light of the TRAIL references and El Etreby (discussed below). Koide describes the use of Mifepristone for treatment of cancers (e.g., leiomyomas, endometriosis, breast cancer, and Cushing's Syndrome) other than prostate cancer. Koide describes that the molecular basis of Mifepristone action is the formation of receptor-progesterone/receptor-mifespristone dimers, which compete with the active progesterone/receptor homodimer, to reduce the effectiveness of the agonist progesterone. Koide at page 553. Thus, Koide suggests that Mifepristone acts in a competitive manner with ligands for the progesterone receptor, but provides no basis for inferring how this competition may be used to promote the effects of other chemotherapeutic agents, such as TRAIL, to increase the apoptotic effect of such agents. Additionally, Applicant maintains that studies in other types of cancer such as leiomyomas, endometriosis, breast cancer, and Cushing's Syndrome, provide little basis for treatment of prostate cancer, due to the very different nature of cancer biology in different cell types.

El-Etreby

El Etreby describes that Mifepristone can exhibit anti-tumor activity in androgen-sensitive and androgen-insensistive cells. El Etreby also describes that mifespristone may be associated with apoptosis. However, the experiments in El Etreby do not measure apoptosis or other cellular markers, but only show the effects of Mifespristone on tumor growth and tumor volume. El Etreby also does not describe or suggest the use of TRAIL for inhibition of prostate cancer. Also, El Etreby is primarily concerned with

the development of agents for the treatment of androgen-insensitive prostate cancer cells, and does not describe, teach, or suggest that Mifepristone, or other antiprogestins, may be used to increase the sensitivity of androgen-sensitive prostate cancer cells, such as LNCaP cells, to TRAIL, or that compositions having this ability may be clinically important. Nor, does El Etreby, in combination with Bonavida, Gliniak, Yu, or Koide describe, teach or suggest that antiprogestins, such as Mifepristone, may act in a synergistic manner with TRAIL, at the level of the TRAIL pathway.

The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. See e.g., *In re Baird,* 16 F.3d 380, 382 (Fed. Cir. 1994); MPEP 4144.08. Applicants assert that the nature of the various agents used in combination with TRAIL as described by Bonavida and Gliniak (e.g., actinomycin D, a general transcription terminator; Adriamycin, an antibiotic; cyclohexamide, a general inhibitor of protein translation; and CPT-11, an inhibitor of DNA topoisomerases) describe a very large genus of chemotherapeutic agents. Even if such compounds can, in certain cases, act as inducers of apoptosis or inhibitors of anti-apoptosis, there is little suggestion that such agents can be used interchangeably with an antiprogestin such as Mifepristone. Koide and El Etreby only add that antiprogestins are specific to certain progesterone-receptor mediated cancers, providing an additional basis for distinguishing antiprogestins from the chemotherapeutic agents used by Bonavida and Gliniak. Thus, one would not be motivated to substitute an antiprogestin for actinomycin D (as used by Bonavida) or CPT-11 (as used by Gliniak) for the treatment of a particular cancer.

Additionally, it is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983). Applicants assert that Bonavida and Yu each describe completely different mechanisms for activation of TRAIL on prostate cancer cells and thus, there would be little motivation to combine the teaching of these references. Also, Yu and Gliniak appear to conflict with at least some of the conclusions of Bonavida. Thus, in contrast to Bonavida, Yu finds that TRAIL mediated apoptosis in prostate cancer cells is mediated by death receptors. Also, Gliniak appears to teach away from Bonavida, indicating that agents, such as adriamycin, that can inhibit apoptotic enzymes in myeloma as taught by Bonavida, are

not effective in increasing the effectiveness of TRAIL in colon cancer cells. Finally, El Etreby provides studies to show that Mifespristone can retard tumor growth in prostate cancer, but does not suggest the use of Mifespristone in combination with TRAIL.

An invention may not be deemed obvious where the prior art only provides an invitation to explore, and does not teach or suggest the Applicant's claimed invention. *In Ex parte Obukowicz*, 27 USPQ 2d 1063 (1992). Thus, the courts have held that an obviousness rejection may not be predicated on the view that the invention was "obvious to try," as for example, where the art gives only general guidance as to the particular form of the invention or how to achieve it. *In re Lindell*, 385 F.2d 453 (CCPA 1967), and *Ex parte Levengood*, 28 USPQ 1300 (Bd. Pat. App. & Inter, 1993). Although both TRAIL and Mifepristone had been used individually with some efficacy in treating prostate cancer, there was no indication, based on the results in the cited art, that the combination of TRAIL and Mifepristone would increase TRAIL-mediated apoptosis in prostate cancer cells at a level that is greater than additive for the effects of each agent alone.

In contrast to the cited references, Applicant describes compositions that act to sensitize cells to TRAIL by specifically activating the DR4/DR5 death receptor pathway, such that the effects seen with the compositions of the invention (i.e., including TRAIL and an antiprogestin) is greater than that of either agent alone. The Examiner has stated that the limitation of formulating a composition having TRAIL and an antiprogestin so as to induce apoptosis in cells that are resistant to either agent is an intended use for the composition. Office action at pages 5-6. The Applicant respectfully asserts that the formulation of a composition that has TRAIL polypeptide and an antiprogestin to provide a composition having increased efficacy is not an intended use, but a quality of the composition itself that renders the composition a chemotherapeutic agent that provides surprising advantages of over compositions of the prior art.

Thus, Applicant's specification teaches that not all prostate cancer cells are sensitive to TRAIL (see Figure 1 of Applicant's specification). For example, as taught by Applicant's specification, TRAIL does not result in a significant increase in apoptosis and/or DR5 expression in certain LNCaP androgen sensitive prostate cells. Also, such cells are not sensitive to Mifepristone at the levels used by Applicant (see the specification, FIG. 1A, 1C). As described in Applicant's specification, both TRAIL and

Mifepristone act via death domain receptors DR4 and DR5 to stimulate of caspase 8, which subsequently activates procaspases 3, 7, and 9. Applicant is therefore able to use Mifepristone to sensitize cells to TRAIL by activating the DR4/DR5 pathway. In this way, Applicant's methods maintain specificity for the TRAIL pathway for induction of cell death by an apoptosis-specific pathway. This is in contrast to the agents proposed by Bonavida and Gliniak which act by non-receptor-mediated mechanisms that are much more generalized to induce cell death and thus, can result in non-specific side effects.

The challenge in prostate cancer is to develop agents that are effective in treating both androgen-sensitive prostate cells and androgen-insensitive prostate cancer cells. Applicant respectfully asserts that the results of Gliniak and Koide using cancers that are not prostate cancer do not teach or suggest the use of TRAIL and Mifepristone for treating prostate cancer. Nor do the studies of Yu indicate how TRAIL and/or an antiprogestin may be used to treat prostate cancer in those prostate cancer cells that are not sensitive to TRAIL. Nor do the studies of either El Etreby in combination with Yu teach how TRAIL may be used to treat prostate cancer cells that are refractory to Mifepristone.

For these reasons, Applicant respectfully asserts that the Examiner has not established a *prima facie* case of obviousness under 35 U.S.C. § 103 (a), and respectfully requests that the rejection be withdrawn.

B. Secondary Considerations

Without in any way acquiescing that the Examiner has established a *prima facie* case of obviousness, Applicant respectfully asserts that secondary considerations further substantiate that Applicant's claimed composition is not obvious in view of the cited references. Applicant submits herein a declaration under 37 C.F.R. § 1.132 describing why these secondary considerations render the composition patentable under 35 U.S.C. § 103(a).

i. Surprising Results

First, the non-obviousness of Applicant's invention is substantiated in view of the surprising results found by Applicant that: (1) that TRAIL and Mifepristone may be used to induce apoptosis in both androgen responsive and androgen independent prostate

cancer cells; (2) combining TRAIL and an antiprogestin such as Mifepristone is synergistic; and (3) that antiprogestins specifically act on the TRAIL pathway.

The Examiner stated that:

> Although the references do not specifically teach that the combination of TRAIL and an antiprogestin or Mifepristone would have a synergistic effect, however, the claimed composition appears to be the same as the composition taught by the combined prior art, absent a showing of unobvious differences. . . . See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex Parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Office Action at page 10.

Ex Parte Gray addressed the situation where the Board of Patent Appeals and Interferences found that purified recombinant nerve growth factor (NGF) was not, as a product by process, patentably distinct from naturally occurring NGF. *In re Best* addresses whether a particular zeolite compound is patentably distinct from the same zeolite compound made by a variation of the method in which the cooling step was not specifically described but would have inherently occurred in substantially the same manner.

Unlike the cases cited by the Examiner, Applicant's composition is not substantially similar to a composition of the prior art. Thus, as described above, Applicant was the first to combine Mifepristone and TRAIL in such a manner such that Mifepristone sensitizes prostate cancer cells to the effects of TRAIL. Both Bonavida and Gliniak describe that other chemotherapeutic agents (e.g. Adriamycin D, cycloheximide, actinomycin D, CPT-11) can interact with TRAIL in a synergistic manner to overcome resistance of the cells the effects of TRAIL. Still, for the reasons discussed above, Applicants assert that there was no suggestion in the art that Mifepristone would act in a similar manner as Adriamycin D, cycloheximide, actinomycin D, or CPT-11.

As noted above, the challenge in prostate cancer is to develop agents that are effective in treating both androgen-sensitive prostate cells and androgen-insensitive prostate cancer cells. Thus, prostate cancer is unique in that the response of these two different cell types to certain chemotherapeutic agents can limit treatment of the cancer. Although Yu and Bonavida describe the use of TRAIL to induce apoptosis in androgen

independent cancer cells, Applicant was the first to discover that Mifepristone can increase the efficacy of TRAIL in inducing apoptosis in androgen-sensitive prostate cancer cells that are resistant to the apoptotic effects of TRAIL. Thus, as shown in Figure 1 of Applicant's specification, treatment of LNCaP cells with 400 ng/ml TRAIL does not alter cell survival significantly. Also, such cells were not sensitive to Mifepristone (see e.g., Figure 1A and 1C). However, treatment of LNCaP cells with Mifepristone followed by TRAIL results in a significant decrease in cell survival (Figure 1A and 1C).

Also, as shown by Applicant's specification, the combination of Mifepristone and TRAIL results in effects that are more than additive, but that display synergy. Thus, as shown in Figure 1A , for LNCaP cells at 16 h, the combination of Mifepristone plus TRAIL results in a substantially greater reduction in survival (down to 40% survival or 60% cell death) than the individual reduction for TRAIL (down to 80% survival or 20% cell death) plus Mifepristone (> 95% survival or < 5% cell death). Similar results are seen for the measurement of apoptosis using the Apoptosense assay (Figure 1C) that measures cytokeratin exposed as a result of apoptosis. Thus, after 16 hours, the measured levels of cytokeratin 18 for the combination treatment of TRAIL and Mifepristone was about 2.9 units (U) cytokeratin 18 per μg total protein, whereas individually, TRAIL resulted in about 0.6 U/μg and Mifepristone resulted in about 1 U/μg. Such synergy would not be anticipated in view of the finding that Mifepristone acts interacts directly with the TRAIL pathway.

Applicant respectfully asserts that there is nothing in the cited references that teaches or suggests the surprising synergy exhibited by the combination of TRAIL and Mifepristone, or that the combination of TRAIL and Mifepristone would be effective to treat prostate cancer cells that are refractory to TRAIL alone. For at least the above reasons, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.

ii. Long-Felt Need

Also, the composition of Applicant's invention provides a means to kill both androgen-sensitive and androgen-insensitive prostate cancer cells. By providing a composition utilizing low doses of TRAIL and an antiprogestin, potentially toxic effects of either compound are avoided. Prostate cancer is one of the most commonly diagnosed

malignancies in men, and a leading cause of cancer-related death. Prostate cancer is a multi-focal disease with clones of androgen-sensitive and androgen-refractory cells existing in a cancer. Although androgen depletion therapy often results in regression of the tumor, a small number of androgen-dependent prostate cancer cells are often able to develop into androgen-independent cells. Also, many androgen responsive cells are very aggressive; thus, there is a compelling need for killing these cells as well as androgen insensitive cells. Thus, there is a long-felt need to be able to target both types of cells, androgen-sensitive and androgen-insensitive, so as to prevent the less invasive and less metastatic androgen sensitive cells from developing into androgen insensitive cells. Although both TRAIL and Mifepristone had been used to reduce proliferation of prostate cancer cells, Applicant's invention provides a means to more effectively kill both androgen-sensitive and androgen-insensitive prostate cancer cells, using reduced doses of TRAIL and Mifepristone, than either agent alone.

Rejoinder of Withdrawn Claims

Withdrawn process claims that depend from, or otherwise include all of, the limitations of an allowable product claim may be rejoined in accordance with the provisions of MPEP § 821.04, and such amendments will be entered as a matter of right if presented prior to allowance. Applicant has amended claims 2-12, 16-22, 25 and 26 to include the limitations of the product claims. Applicant respectfully asserts that as amended, the withdrawn claims are in a form suitable for immediate allowance, and request reentry of the amended method claims 2-12, 16-22, 25 and 26 into the application.

CONCLUSION

In view of the foregoing amendment and remarks, each of the claims remaining in the application is in condition for immediate allowance. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the outstanding rejections. The Examiner is respectfully invited to telephone the undersigned at (336) 747-7541 to discuss any questions relating to the application.

Respectfully submitted,

Date: July 21, 2006

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